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SOME CLINICAL ASPECTS OF THE BIOELECTRICS AND ELECTROCHEMISTRY OF MYOCARDIUM*

CHARLES E. KOSSMANN

Associate Professor of Medicine
New York University College of Medicine, New York, N. Y.

IT IS OFTEN stated that the Physiology of today is the Medicine of tomorrow. Mine is the prophetic task of bringing to a clinical level what is known about the transmembrane potential and its electrolytic origin. The adjective prophetic is used advisedly because, between the Physiology of today and the Medicine of tomorrow, there is obviously a time parameter which has not yet elapsed. However, my talk will not be one entirely of prophesy, because if it be true that the Physiology of today is the Medicine of tomorrow, it is also true that the Medicine of today is the Physiology of tomorrow. This may make it possible for me to attire some old medical facts in new and shining physiological raiment and perhaps strip a few clinical fancies of their tattered and long since outmoded cloaks of ignorance.

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From the Department of Medicine, New York University College of Medicine, the Electrocardiographic Laboratory of the Third (N.Y.U.) Medical Division of Bellevue Hospital, and the Cardiovascular Service and Heart Station, Lenox Hill Hospital, New York, N. Y.

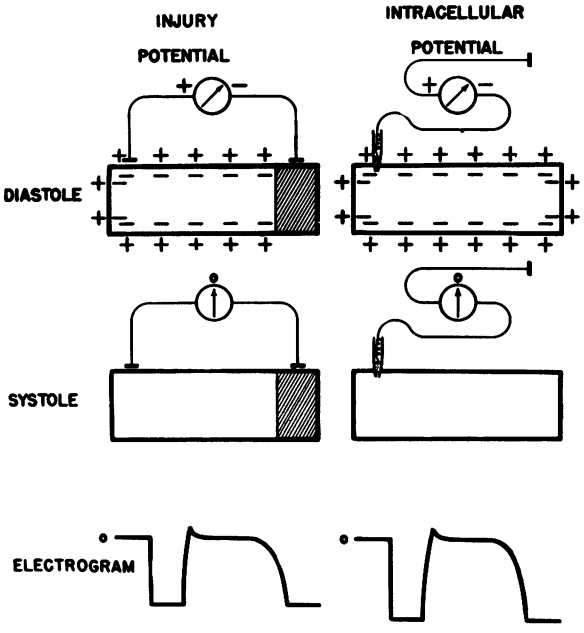

Figure 1. Diagram to illustrate the similarity of electrograms obtained by recording the injury potential (shaded area of cell is injured, e.g., depolarized) and the intracellular potential. The second electrode, when recording the latter, is assumed to be in a surrounding conducting medium distant from the cell. The smaller magnitude of the injury electrogram is the result of loss of potential by short circuit through the surrounding medium. (From Kossmann, in *Advances in Electrocardiography*[4]. This Figure, together with Figures 2 and 6, reproduced by permission of the author and the publisher, Grune & Stratton, Inc., New York.)

Clinical Aspects of the Membrane Action Potential

That the action potential of the myocardial cell of animals had the approximate monophasic form shown earlier this evening* was known since the time of Matteucci[1]. In man, a reasonable facsimile has been obtained by means of the intracardiac catheter-electrode when this electrode is pressed against the endocardium. Pressure or touch potentials of this kind have been obtained in all four chambers of the human heart[2]. The origin of these touch potentials, consisting as it does of excitation block[3] at the electrode, is somewhat different than is the case for the monophasic action potential of the older physiologists. Their records were obtained by pairing a healthy end of a muscle strip through a galvanometer to an injured end. The approximate experiment, reduced for simplicity to a single cell[4], is shown on the left of Figure 1.

* Hoffman, B.F. Electrophysiology of Single Cardiac Cells, *Bull. N. Y. Acad. Med.* vol. 35, 689-709, Nov. 1959.

Actually, in making such a record of the injury potential, there is current flowing during diastole from the uninjured to the injured portion. When depolarization of this cell or group of cells occurs (labeled "systole" in the figure), all of this current of injury is dissipated and the recorder returns to zero from the less than zero level originally created by the current. The electrogram thus obtained is shown diagrammatically in the lower part of the figure on the left.

When the intracellular electrode is used, as on the right, the curve obtained is similar in form, though relatively larger for a comparable cell, since little or no current is flowing from the outside to the inside of the membrane as in the first preparation. It will be noted, too, that the connections to the galvanometer in the latter instance are the reverse of those in the former, and that the indifferent electrode is in the conducting medium surrounding the preparation.

It can readily be appreciated, upon examining the diagram on the left, how it came to be believed that excitation consisted of a wave of negativity when, in truth, what the early physiologists were observing was a reduction in the positivity of the outside of the cell during its active phase. This gave rise to the "negativity hypothesis" of electrical excitation of muscle. It is interesting that such a concept was held for many years because of an invalid interpretation of a valid experiment. The work of Craib[5] and later of Wilson, Macleod and Barker[6] gradually resulted in the universal adoption of the bipolar hypothesis[7], but not without long and at times acrimonious debate. The first recording of the intracellular potential of heart muscle[8,9] finally left no doubt about the true state of affairs in the cell during rest and during activity.

At first glance this physiological history may seem to have no great clinical implication. The truth is that it delayed for a long time the final formulation of principles for the interpretation of the precordial leads when these came into clinical use. In fact, all of us were so influenced by emphasis on negative electricity that in the initial paper on normal, unipolar precordial leads published in 1935[10], the records were made upside down compared to present custom in order to make the intrinsicoid deflection into a "chief upstroke" comparable to the intrinsic deflection of the physiological records of the day. Currently, the subject has been expanded into another controversy which revolves about whether the heart as a whole behaves as a single dipole or as multiple dipoles. This has led to an intensive study of the electric field

around the heart, and to several attempts to prove the dipolar behavior of the heart as a whole by the application of cancellation techniques to the human body[11-15].

At the clinical level, these and other similar investigations all relate to the ultimate solution of a common clinical problem. It is concerned with the answer to the question: Are the electrocardiographic abnormalities which are observed in any given record due to actual intrinsic disease of the myocardium or of the conduction system, or are they due to an unusual position of the heart in the chest? The solution ultimately relates to the establishment of a system of surface leads which will yield quite precisely the spatial electromotive force of the heart, undistorted by the effects of the conducting medium around it, or by its eccentric location within the chest.

I give you this brief review to illustrate how a relatively simple physiological technique, such as the recording of an injury potential, gave rise for a good many decades to a concept which was only gradually corrected by a great variety of observations, and was firmly settled in the end, at least so far as one aspect was concerned, by the development of the microelectrode technique of recording intracellular potentials. It is to be noted, however, that in a fashion characteristic of all biological research, the solution of one problem has given rise to a great many others.

To come to a consideration of pacemaker potentials—it is interesting that since the time of Sir Thomas Lewis, when the electrocardiographic features of a variety of arrhythmias first were described, little progress was made until recently, either in the understanding of the mechanisms involved or in the therapy used for tachycardia, fibrillation or flutter. The records of the transmembrane potential in pacemaker tissue which you have seen bode well for additional progress in this field soon. For reorientation purposes, the monophasic action potential of the sino-atrial node of the rabbit, made by my colleagues, Drs. Kleinfeld and Stein, with the help of Mr. Magin, is shown in Figure 2. As discussed earlier this evening by Dr. Hoffman*, it reveals the characteristic loss of the transmembrane potential during diastole until the firing or threshold level is reached, and only then is the impulse propagated. This diastolic loss of potential is due to the natural incapacity of pacemaker cells to maintain intact impedance during diastole. It would seem reasonable to believe that in the clinical case of tachycardia or premature systoles

* See footnote, page 4

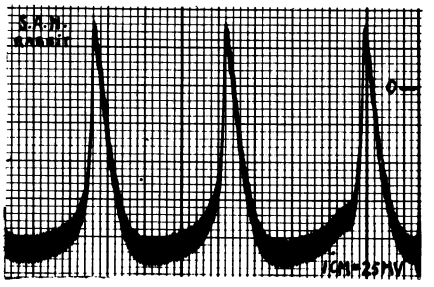

Figure 2. An intracellular potential made from the region of the sino-atrial node of a rabbit, demonstrating the diastolic loss of potential characteristic of pacemaker tissue. Calibration, 1 cm. = 25 mv. Time lines, 0.04 sec. (From Kossmann, in *Advances in Electrocardiography*[4].)

a cell or group of cells somewhere in the heart, either normally or as a result of disease, displays a similar dissipation of the transmembrane potential during diastole and ultimate propagation of an impulse. The speed of this phenomenon will determine in part whether the clinical effect will be extrasystoles, an abnormal rhythm, or a tachycardia.

With regard to circus rhythm, other factors undoubtedly are involved, such as the duration of the refractory period, and here choline plays an important part. This fact has been relearned by the recent experimentation principally of Burn, Williams and Walker[16], but was suspected for a long time as a result of the ease with which fibrillation of the atria could be produced by vagal stimulation in conjunction with other manipulations. At the moment, there is not much in this area of immediate use to the clinician. Nevertheless it would seem prudent to follow these physiological investigations quite carefully, for with increased knowledge of the prepotential, the factors concerned with alteration of the threshold potential, and the relationship of choline, 5-hydroxytryptamine, and probably other naturally occurring agents to the transmembrane potential, there will undoubtedly be advances of eventual use at the bedside.

One of the less satisfactory aspects of clinical electrocardiography is the matter of block, both intraventricular and atrioventricular. Present concepts localize this block to some part of the conduction system. From what has been observed with the microelectrode it would seem that block can be observed at the cellular level. If depolarization of the ventricular cells is slowed, widening of QRS in a surface lead will occur. If depolarization fails completely and in all ventricular cells, then complete block will ensue.

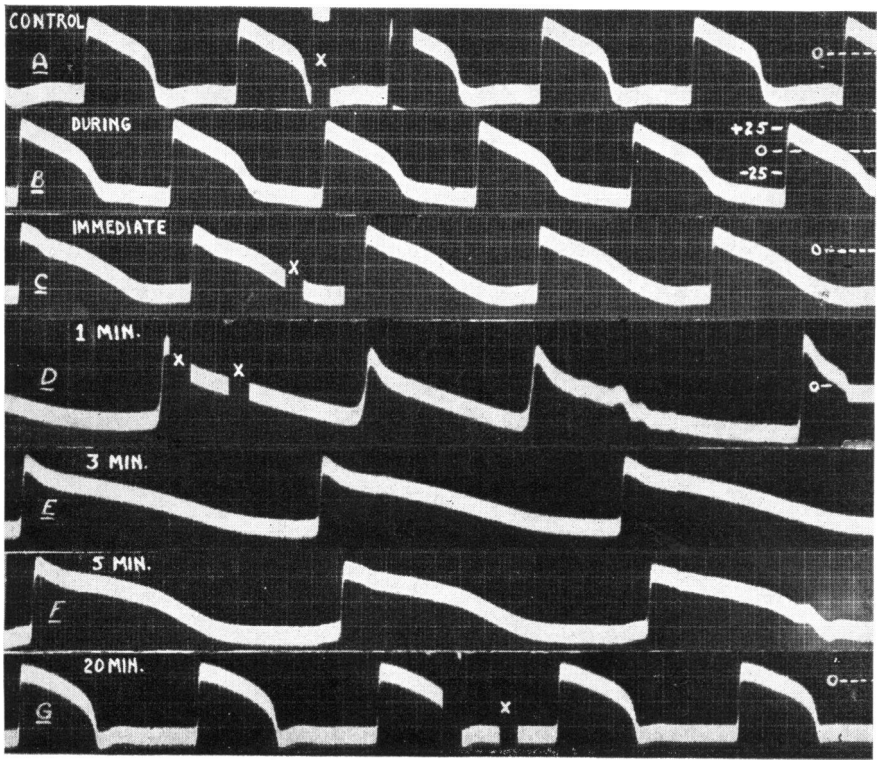

Figure 3. Sequential effects of barium chloride (5 mg./kg.) injected into the aorta on the membrane action potential of ventricular fibers of the frog heart. The prematurity, and long rise time, of depolarization and the smaller resting potential are to be noted in the middle two complexes of record D. (There is artefact on the repolarization phase of the second.) Calibration is shown in record B (0.9 cm. = 50 mv.). Time lines 0.04 sec. X indicate where a standardization voltage was introduced. (From Kleinfeld, Stein, and Meyers[17], *Circulation Res. 2*:488-93, 1954. Reproduced by permission of the authors.)

The evidence for cellular block, as it might be called, is of several types. For example, the action potential of the frog ventricle in Figure 3 illustrates the sequential effects of 5 mg. per kg. of barium chloride injected into the aorta[17]. There is a gradual lengthening of the repolarization process, particularly its third phase, but over a period of 20 minutes there is a return to the control configuration. To be noted is the record taken one minute after injection. In the middle of it are two beats, probably of ectopic origin, since both were premature relative to the remainder. Both of these show a rate of depolarization, and incidentally a magnitude of resting potential, which is somewhat less than in the action potential on either end of the strip. The slowed spike can be interpreted as a partial block of depolarization which should

manifest itself as a widened QRS interval in a surface lead.

Another piece of evidence in this direction is the demonstration of the existence of alternation of the action potential. Alternation both in magnitude and duration of any part of the membrane action potential, including the after-potential, has been observed by Kleinfeld, Stein and Magin[18] in our laboratory. In the case of pacemaker tissue under the influence of a choline esterase inhibitor, alternation of a type may occur in which every second beat fails to reach the threshold level and the intracellular equivalent of 2:1 sino-atrial block develops.

Other agents and procedures can slow the rise time of depolarization. Potassium in high serum concentration does it clinically, and, as used for inducing cardioplegia, can prevent the action potential completely.

All of these observations on different grades of impairment of depolarization suggest that there may be such a spontaneous clinical entity as intraventricular block or even complete block of depolarization at the myocardial level. Certainly many aspects of bundle-branch block and atrioventricular block are most difficult to explain in terms of the conventional point of view. It is visualized that clarification will come only with precise studies such as were presented earlier in this scientific session.

Clinical Aspects of the Interrelations Between Electrolytes and the Transmembrane Myocardial Potential

In the area of electrolytes, relative to clinical behavior of the myocardium, a good deal more can be said of a definitive nature. The most significant advances in the clinic have been made in the field of the interrelationships of potassium, calcium and digitalis. It is perhaps easiest to present them in relation to each other, because ordinarily the effects of digitalis are opposed by potassium and augmented by calcium. The latter is an old clinical observation made in 1936[19], when it was discovered that calcium given intravenously to a digitalized patient could be fatal. This observation seems to have been forgotten or sometimes overlooked during surgery, and it is suspected that on some occasions where cardiac arrest has occurred in the operating room and cardiac massage instituted along with the injection of calcium, the result was unfavorable because it was forgotten that the patient was digitalized.

Hypocalcemia induces fairly characteristic changes in the electro-

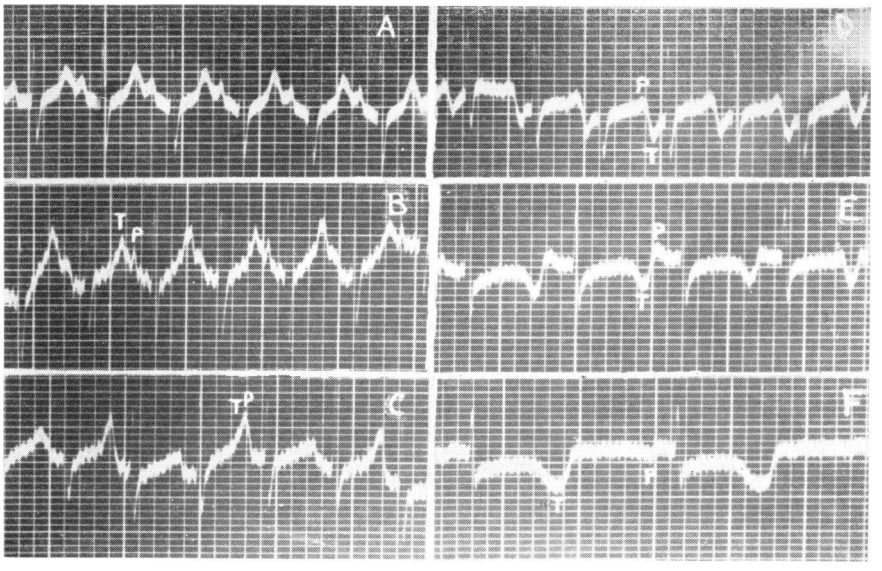

Figure 4. Effects of intravenous EDTA (50 mg./kg.) on lead II of the rabbit electrocardiogram. A, control (rate 333/min., Q-T 0.12 sec., K = 0.28); B, during administration of drug (T waves taller and peaked, Q-T 0.15 sec.; K = 0.36); C, immediately after injection (alteration of T waves, Q-T interval 0.14 sec., K = 0.34); D, 30 sec. after injection (T wave inverted); E, 60 sec. after injection (rate 214/min., Q-T 0.20 sec., K = 0.38, T wave negative); F, 130 sec. after injection (rate 111/min., P wave inverted as a result of shift of pacemaker to A-V node, S-T junction and segment depressed, T inverted, Q-T 0.27 sec., K = 0.37). (Modified from Kleinfeld and Gross[20], *Amer. J. Physiol. 187:* 479-82, 1956. Reproduced by permission of the authors and the publication.)

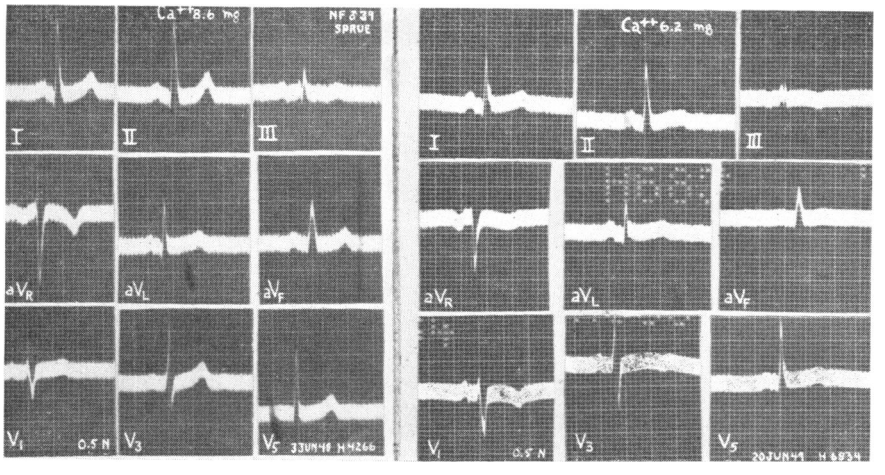

Figure 5. Non-tropical sprue with hypocalcemia in a man 39 years old, admitted for recurrent fractures. The electrocardiogram on the left was recorded when the serum Ca was 8.6 mg./100 ml.; on the right when it was 6.2 mg./100 ml. Although there are differences in the form of the final ventricular deflections between the two records, the Q-T intervals are identical (0.36 sec.) and the systolic indices almost so (0.414, 0.405). The status of the other serum electrolytes was unknown at the time of the recordings but on other occasions these were not abnormal.

cardiogram. Figure 4 illustrates what happens when 50 mg./kg. of ethylenediamine tetra-acetic acid, as the disodium salt, is injected into a rabbit[20]. This chelating agent will remove ionized calcium from the blood stream. A is the control; B is immediately after injection and shows some prolongation of the Q-T interval and a change in form of the T wave; C discloses alternation of the T wave; and D, E, and F, inversion of this deflection. The slow rate in the last record is the result of atrioventricular nodal rhythm. Inversion of the T wave may be seen in the hypocalcemia of spasmophilia in children. In adults the most frequent abnormality is a prolonged Q-T interval, but the magnitude and direction of the recovery process may be altered sufficiently to give some changes in T wave as seen in a case of non-tropical sprue (Figure 5). The hypocalcemic record is on the right, where the T wave in leads V_1 and V_3 is to be compared with the control T wave in these leads on the left. The serum calciums are indicated at the top of each electrocardiogram. Other electrolytes were not measured at the time, but were not abnormal on other occasions. Interestingly, the Q-T intervals in the two records were identical (0.36 sec.) and the systolic indices were 0.414 and 0.405, both within normal limits.

To illustrate an important point, Figure 6 shows what happens when the isolated frog heart is perfused with Ringer's solution, Ringer's solution with half calcium, and finally calcium-free Ringer's solution for different intervals of time[4]. In this preparation the direct cardiac output was simultaneously measured with the ventricular action potential. It will be noticed that the control output was 4.2 ml. per minute, that five minutes after perfusion with half-calcium Ringer's solution the action potential had not changed a great deal, nor had the rate, but that the cardiac output began to fall. Lastly, after a prolonged period of perfusion without calcium, the cardiac output became almost nothing, yet the action potential showed little change, other than some prolongation of the plateau portion of the repolarization phase. This would illustrate what is now fairly well known, namely, that calcium is essential for excitation-contraction coupling. The figure illustrates dissociation of this coupling induced by hypocalcemia.

The known additive effects of calcium and digitalis have led to the development of two clinical tests which may eventually be proven to have some value, although both are potentially hazardous. The first of these is the test described by Gubner and Kallman[21], concerned with

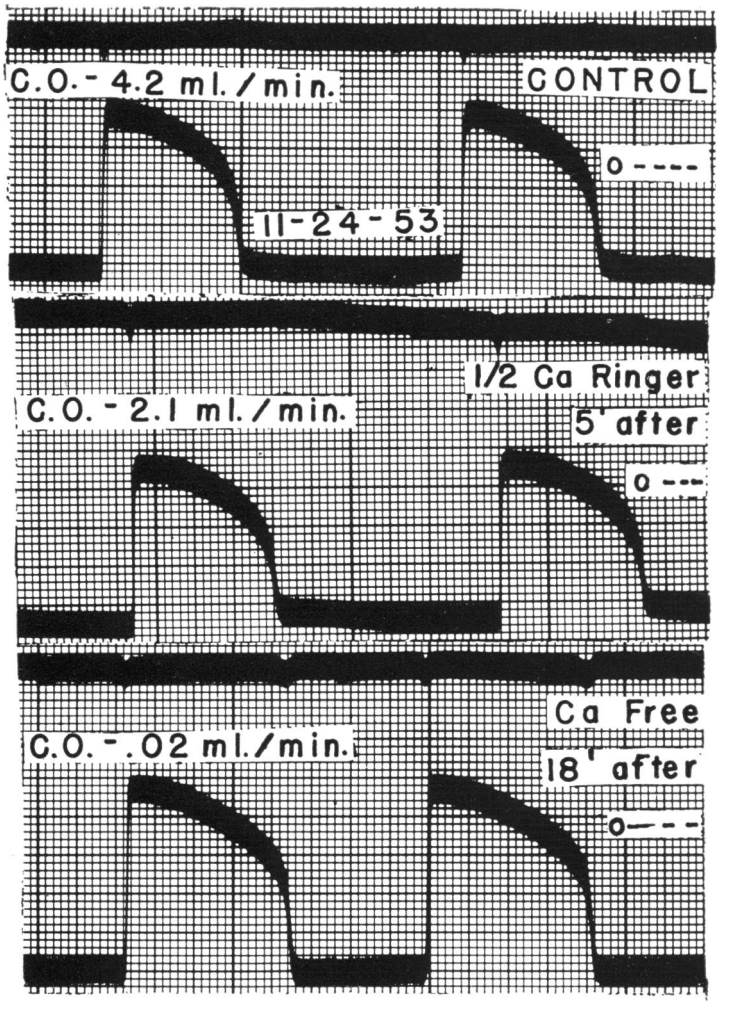

Figure 6. Effect of decreasing the calcium in the perfusing Ringer's solution on the electrical and mechanical activities of the isolated perfused frog ventricle. Simultaneous records are of the indirect bipolar electrocardiogram (above—low amplitude trace) and of the single fiber membrane action potential (below). Cardiac output (C. O.) was determined just before recording the electrical potentials. Time lines 0.04 sec. Calibration for intracellular potential, 0.9 cm. = 50 mv.; for electrocardiogram 1.0 cm. = 1.0 mv. (From Kleinfeld, Ch. 3 in Kossmann's *Advances in Electrocardiography*[4].)

the intravenous injection of the disodium salt of ethylenediamine tetra-acetic acid. The chelating agent will remove ionized calcium from the blood stream. However, to achieve this, a continuous infusion must be given, and the recommended rate is approximately 15 mg. per minute. When this is given to a patient who has the cardiac manifestations of digitalis toxicity, these manifestations during the course of the infusion

may disappear. The clinical application of the test would be to demonstrate that an arrhythmia or some other abnormality in the record is in truth due to digitalis rather than intrinsic disease, and at the same time to terminate a potentially dangerous toxic rhythm if this should be present.

Another clinical procedure, the calcium-digitalis tolerance test, has been described in some detail by Nalbandian, Gordon and Kaufman[22]. This test is an endeavor to quantitate the degree of digitalization of a patient. It is the reverse procedure of the EDTA test, calcium being given intravenously as a 10 per cent solution of $CaCl_2$ in progressively larger increments. This is done over a period of 20 minutes or until such time as distinct evidence of digitalis toxicity appears. The authors have worked out some calculations whereby the percentage of total digitalization in any particular patient can be estimated. The quantitative aspects of the method are indeed attractive but the known hazards of the simultaneous use of calcium and digitalis make it prudent to do additional observations under controlled conditions before the test is accepted for general clinical usage.

Potassium has received more attention at the clinical level than any other electrolyte. The use of it in concentrated form by the surgeon to induce cardioplegia during open heart surgery has already been mentioned. It is most often utilized by the medical man in the treatment of digitalis toxicity, and almost every clinician is aware of the usefulness of this drug in eliminating or decreasing the toxic effects of digitalis, especially in the patient with advanced heart disease. The frequent occurrence of atrial tachycardia with 2:1 A-V block as a manifestation of digitalis toxicity, which may be relieved by potassium even though the serum potassium may be normal, is something which has been called to our attention by Lown and Levine[23].

The distinctive effects of potassium on the intracellular potential are mirrored quite comparably in the clinical electrocardiogram. A few examples should suffice, since these effects are fairly well known. First, with reduction in the potassium content of the serum and probably of the myocardium, there tends to be a reciprocal change in the U wave and in the T wave. As the potassium falls, the T wave goes down, often to inversion. Downward displacement of the S-T segment may also occur. Conversely, the U wave becomes more prominent. It was Surawicz and Lepeschkin[24] who called attention to the clinical fact that the

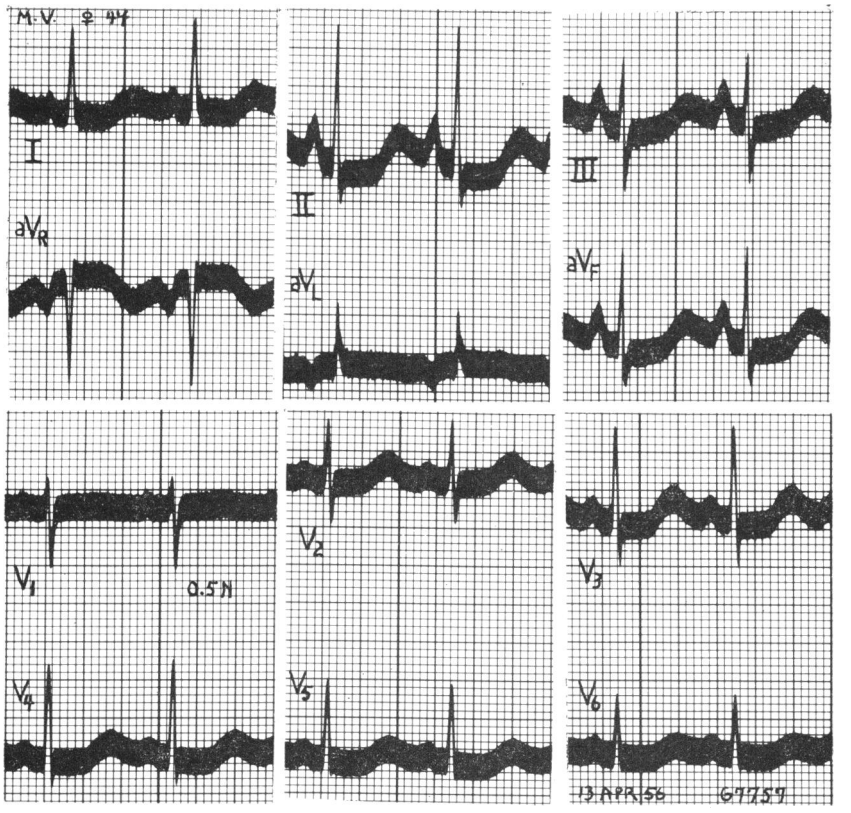

Figure 7. Electrocardiogram of a 44 year old white female (M. V.) with duodenal obstruction and vomiting for 3 weeks. The electrolyte pattern was of hypokalemic alkalosis (Table I). (From Kossmann[25], *Trans. Life Insce. med. Dir. Amer.* This Figure and Figure 8 reproduced by permission of the publisher.)

TABLE I. Table showing the time of recording the electrocardiograms of patient M. V. reproduced in Figs. 7 and 8 in relation to the serum electrolytes and BUN before (13 Apr. '56) and after the institution of corrective therapy. (From Kossmann[25]. Reproduced by permission of the publisher.)

Pt. M. V. ♀ *44*	*13 Apr. 56*	*15 Apr. 56*	*17 Apr. 56*	*18 Apr. 56*
EKG	Abnormal	.....	Normal	.....
BUN	37.1*	21.4	.....	23.7
Na	138.0	135.0	.....	135.0
K	2.0	2.8	.....	4.8
Cl	.....	86.9	.....	97.6
HCO_3	52.2	34.0	.....	27.3
Ca	11.1	.....	.....	.....
P	3.8	.....	.....	.....

* BUN, Ca and P in mg./100 ml.; others in mEq./L.

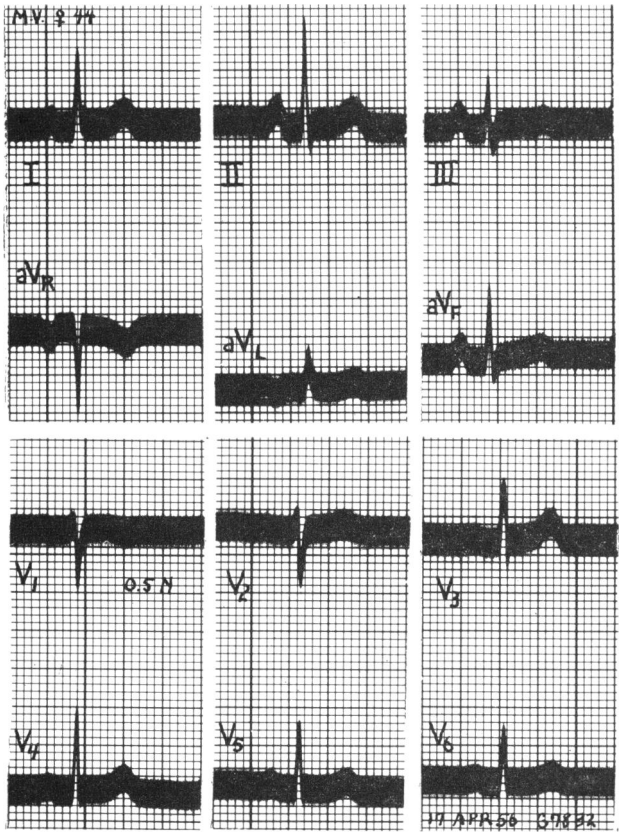

Figure 8. Normal electrocardiogram of patient M. V. recorded four days after the one shown in Fig. 7, and after the correction of hypokalemia, alkalosis, and azotemia. (From Kossmann[25].)

duration of the Q-T interval was actually not prolonged in potassium deficiency, but rather that it appeared to be prolonged simply because the U wave, related to the after-potential of intracellular records, was exaggerated.

It is not ordinarily appreciated how striking these changes may be in the clinical electrocardiogram, and to illustrate this I show the following (Figure 7) record of a young woman who was vomiting for a period of three weeks as a result of pyloric obstruction[25]. As you can see, the changes, especially in the S-T segment, T wave, and not easily discerned U wave, are most pronounced, and if the record were seen by itself, it might not be suspected of being on the basis of simple electrolytic disturbance. The biochemical and electrolytic data, which indicate the existence of a hypokalemic alkalosis at the time of the first

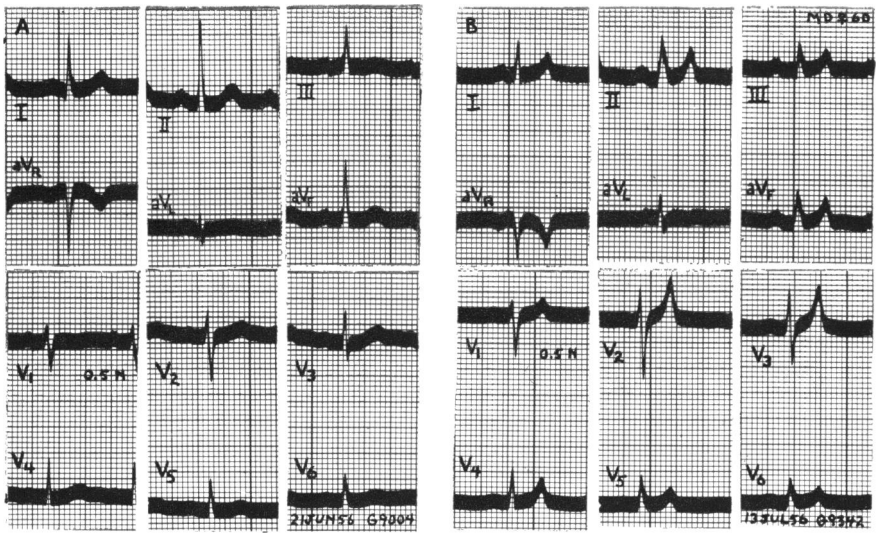

Figure 9. Electrocardiograms of a 60 year old white female before (A, 21 Jun. '56) and after (B, 13 Jul. '56) subtotal gastrectomy with duodenal drainage performed on 25 Jun. '56. Because of bleeding, she received 13 units before and just after operation. Between 9 Jul. '56 and 12 Jul. '56 she received 1 liter of 5 per cent dextrose in distilled water daily, with 40 mEq. of potassium added to the last bottle. The abnormal record, B, shows the characteristic lowering of the voltage of QRS, widening of the QRS interval, shortening of the Q-T interval, and sharply pointed high T wave when the serum K was 6.8 mEq./L. (see Table II).

TABLE II. Biochemical data obtained on patient M.D., a 60 year old woman whose electrocardiograms are shown in Figure 9. To be noted are the abnormalities on July 13, which was the day of the abnormal electrocardiogram of Figure 9B. The principal abnormalities were azotemia, hyponatremia, hyperkalemia, hypochloremia and acidosis.

Pt. M.D. ♀ *60*	IATROGENIC HYPERKALEMIA				
	21 Jun.	*26 Jun.*	*3 Jul.*	*6 Jul.*	*13 Jul.*
EKG	Normal	.....	.....	.....	Abnormal
BUN	11.7*	.....	30.6	19.0	71.2
Na	.....	139.0	131.0	131.0	118.0
K	.....	3.3	4.7	4.3	6.8
Cl	.....	104.3	104.2	103.8	87.1
HCO_3	.....	27.3	24.0	23.1	19.7

* Units as in Table I.

electrocardiogram, and its gradual correction by therapy, are shown in Table I. The electrocardiogram taken four days after the first (Figure 8) is completely normal at a time when there has been re-establishment of normal serum potassium and dissipation of the alkalosis.

In contrast, the effects of high potassium, also well known, are

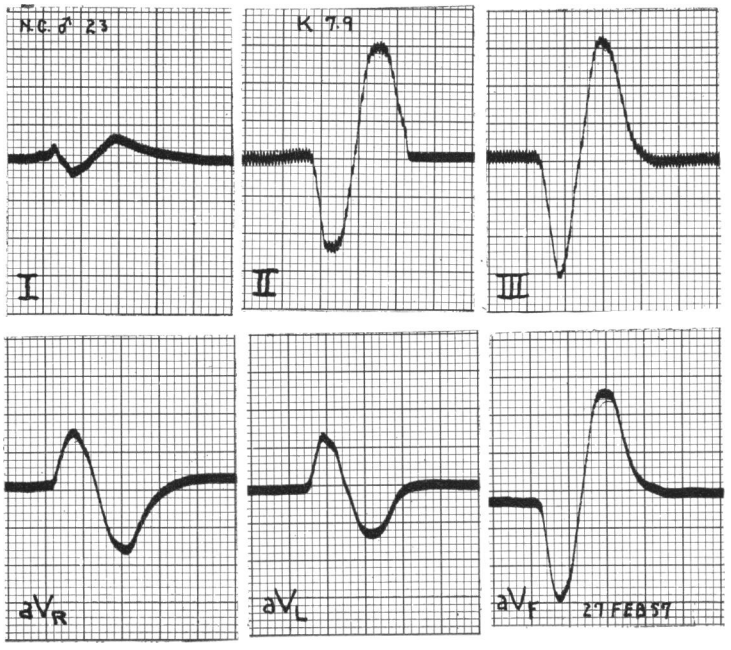

Figure 10. Terminal electrocardiogram of a 23 year old male heroin addict who, while in jail, attempted suicide by hanging four days before. A lower nephron nephrosis developed and on the day of the electrocardiogram and death the following blood chemistries were obtained: K 7.9 mEq./L.; BUN 180 mg./100 ml.; pH 7.27; CO_2 8.71 mEq./L. To be noted are the bizarre, wide QRS complexes fusing imperceptibly into the final ventricular deflections, the opposite directions of the initial and final ventricular deflections, and the absence of evidence of atrial activity. The rate of the idioventricular pacemaker was less than 50 beats per minute and irregular.

illustrated in Figure 9 and Table II. The earliest change seen is a shortening of the Q-T interval and a greater sharpness of the T waves (Figure 9B). This fits in with the shortening of the repolarization process of the intracellular record when the extracellular potassium is increased. In more advanced stages of the situation there is an increase in the duration of intraventricular conduction and continued shortening of the recovery period, so that one gets the easily recognizable picture of a long QRS interval with a short Q-T interval (Figure 9B). An illustration of these effects is well shown in Figure 9 since a control record was available (Figure 9A). This 60 year old white woman had a subtotal gastrectomy with duodenal drainage. In addition to early postoperative transfusions she was given intravenous fluids from 9 July to 12 July consisting of 5 per cent dextrose in distilled water, with added potassium on one occasion but no sodium. The results of this therapy on the serum electrolytes are shown in Table II, and the elec-

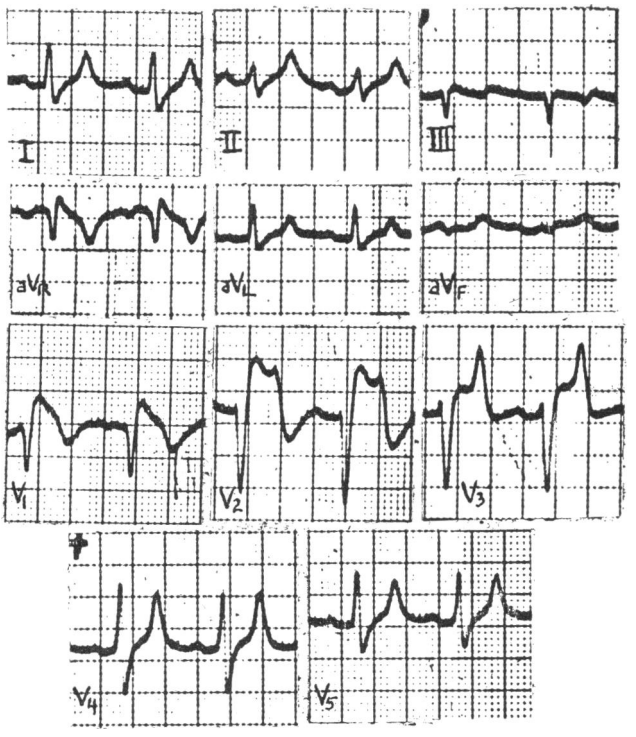

Figure 11. Postcholecystectomy transfusion reaction with lower nephron nephrosis and hyperkalemia in a 43 year old male. A few days before the above electrocardiogram was made, the BUN was 146 mg./100 ml. and the K 6.6 mEq./L., but the electrocardiogram was still normal. After dialysis on the artificial kidney the above abnormalities, consisting of a wide QRS interval, a short Q-T interval, and unusual elevation of the S-T segments in leads V_1 to V_3 disappeared. The patient went on to die, but showed no evidence of myocardial disease at necropsy. (Reproduced by courtesy of Dr. Calvin Kay of Philadelphia.)

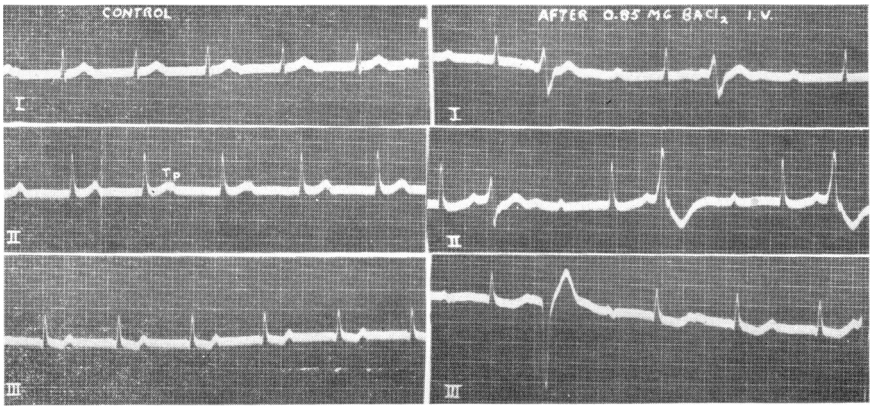

Figure 12. Effect of intravenous Ba Cl_2 (0.85 mg.) in a male patient in his middle fifties with no evidence of heart disease other than a prolonged P-R interval (0.44 sec.). The drug had no effect on the latter except to prolong it slightly (0.46 sec.), but did cause evanescent ventricular premature systoles with coupling.

trocardiographic alterations caused by the iatrogenic hyperkalemic acidosis are shown in Figure 9B. In the agonal stages the QRS and T may be quite bizarre and atrial activity not apparent (Figure 10). An interesting record is the next one, which was lent to me by Dr. Calvin Kay of Philadelphia (Figure 11). It was taken on a man who, after a cholecystectomy, went into shock and developed a lower nephron nephrosis. The record that you see was taken at a time when the BUN and the serum potassium were abnormally high. It shows unusual elevation of the S-T segment in leads V_1 to V_3, an abnormality which is occasionally seen in hyperkalemia. This patient, at the time, was suspected of having some intrinsic cardiac disease as well as azotemia. He was placed on the artificial kidney with a temporary restitution of a normal electrolyte balance; the electrocardiogram then became entirely normal. Levine, Wanzer and Merrill[26] observed this reversal of the S-T displacement of hyperkalemia some time ago and have spoken of it as the "dialyzable current of injury". Parenthetically, despite the therapy, this patient died, and at necropsy showed no evidence of organic disease of the coronary arteries or of the myocardium.

There are other electrolytes which may prove to have greater clinical importance than they do at present, by virtue of the studies being made of them and their effects on the transmembrane potential. I have already shown one experimental effect of barium (Figure 3). Older clinicians will remember that in the early 1930's barium was suggested as a drug to be used in complete heart block. I show you one record (Figure 12) of a man who had only incomplete A-V block, but we made a great many observations on him with varying oral and intravenous doses of barium. All that the drug did was to produce extrasystoles, which theoretically may be of use with a faulty idioventricular pacemaker, but had little effect, in this one patient, on atrioventricular conduction.

The popularity of molar sodium lactate for the treatment of complete heart block, as far as I know, has not been studied at the membrane level, but it would seem that the change in pH of the perfusion milieu produced by this agent must have effects on the impedance of the myocardial membrane and the gradient of ions that exists across it.

We have some observations also on the effects of cadmium and of lithium[27, 28], and others have data on magnesium and strontium[29-31], but since these, with the exception of magnesium, have no immediate clinical application, I shall not discuss them at this time.

SUMMARY

There can be no question that the newer physiology of the myocardium as revealed here today will be a most important part of the Medicine that we practice tomorrow. I hope I have demonstrated, too, that the Medicine of yesterday has at least pointed the way in many instances to approaches and paths of investigation which today are yielding such fruitful results by the superb techniques available for measuring intracellular potentials and the gradients, fluxes, and exchanges of electrolytes across the myocardial membrane. Although those of us primarily concerned with the health of the whole man can only have feelings of inferiority in the presence of those who have mastered such quantitative physiological methods, we can take solace in the knowledge that good research is good whether done on the whole man or on the membrane of one of his cells. By means of continued, painstaking clinical observation, in terms of the physiological data and methods available, the Medicine of today, as in the past, can contribute weightily to the Physiology of tomorrow.

REFERENCES

1. Matteucci, C. Note sur les phénomènes électriques des animaux, *C. R. Acad. Sci. 13*:540-41, 1841.
2. Kossmann, C. E. The electrocardiographic effects of myocardial and pericardial injury, *Bull. N. Y. Acad. Med. 28*:61-89, 1952.
3. Wilson, F. N., Hill, I. G. W. and Johnston, F. D. The interpretation of the galvanometric curves obtained when one electrode is distant from the heart and the other near or in contact with the ventricular surface: Part I. Observations on the cold-blooded heart, *Amer. Heart J. 10*:163-75, 1935. Part II. (Wilson, F. N., Johnston, F. D. and Hill, I. G. W.). Observations on the mammalian heart, *Amer. Heart J. 10*:176-89, 1935.
4. Kossmann, C. E. *Advances in electrocardiography.* New York, Grune & Stratton, 1958.
5. Craib, W. A study of the electrical field surrounding active heart muscle, *Heart 14*:71-109, 1927.
6. Wilson, F. N., Macleod, A. G. and Barker, P. S. *The distribution of the currents of action and of injury displayed by heart muscle and other excitable tissues.* Ann Arbor, U. of Michigan Press, 1933.
7. Macleod, A. G. The electrogram of cardiac muscle: I. An analysis which explains the regression or T deflection, *Amer. Heart J. 15*:165-86, 1938. II. The lengths of the stages of activity, *Amer. Heart J. 15*:402-13, 1938.
8. Coraboeuf, E. and Weidmann, S. Potentiels d'action du muscle cardiaque obtenus à l'aide de microélectrodes intracellulaires. Présence d'une inversion de potentiel, *C. R. Soc. Biol. 143*:1360-61, 1949.
9. Woodbury, L. A., Woodbury, J. W. and Hecht, H. H. Membrane resting and action potentials of single cardiac muscle fibers, *Circulation 1*:264-66, 1950.
10. Kossmann, C. E. and Johnston, F. D.

The precordial electrocardiogram. I. The potential variations of the precordium and of the extremities in normal subjects, *Amer. Heart J. 10*:925-41, 1935.

11. Schmitt, O. H., Levine, R. B. and Simonson, E. Electrocardiographic mirror pattern studies: I. Experimental validity tests of the dipole hypothesis and of the central terminal theory, *Amer. Heart J. 45*:416-28, 1953. II. (Levine, R. B., Schmitt, O. H. and Simonson, E.). The statistical and individual validity of the heart dipole concept as applied in electrocardiographic analysis, *Amer. Heart J. 45*:500-18, 1953. III. (Simonson, E., Schmitt, O. H., Levine, R. B. and Dahl, J.). Mirror pattern cancellation in normal and abnormal subjects, *Amer. Heart J. 45*:655-64, 1953.
12. Frank, E. Measurement and significance of cancellation potentials on the human subject, *Circulation 11*:937-51, 1955.
13. McFee, R. and Johnston, F. D. Electrocardiographic leads: I. Introduction, *Circulation 8*:554-68, 1953. II. Analysis, *Circulation 9*:255-66, 1954. III. Synthesis, *Circulation 9*:868-80, 1954.
14. Brody, D. A. and Copeland, G. D. Electrocardiographic cancellation: some observations concerning the "nondipolar" fraction of precordial electrocardiograms, *Amer. Heart J. 56*:381-95, 1958.
15. Burger, H. C. Lead vector projections. I. *Ann. N. Y. Acad. Sci. 65*:1076-87, 1957.
16. Burn, J. H., Vaughan Williams, E. M. and Walker, J. M. The production of block and auricular fibrillation in the heart-lung preparation by inhibitors of cholinesterase, *Brit. Heart J. 17*:431-47, 1955.
17. Kleinfeld, M., Stein, E. and Meyers, S. Effects of barium chloride on resting and action potentials of ventricular fibers of the frog, *Circulation Res. 2*: 488-93, 1954.
18. Kleinfeld, M., Stein, E. and Magin, J. Electrical alternans in single ventricular fibers of the frog heart, *Amer. J. Physiol. 187*:139-42, 1956.
19. Bower, J. O. and Mengle, H. A. K. The additive effect of calcium and digitalis, *J. Amer. med. Assoc. 106*:1151-53, 1936.
20. Kleinfeld, M. and Gross, M. Electrocardiographic manifestations of hypocalcemia produced with ethylenediamine tetraacetic acid, *Amer. J. Physiol. 187*: 479-82, 1956.
21. Gubner, R. S. and Kallman, H. Treatment of digitalis toxicity by chelation of serum calcium, *Amer. J. med. Sci. 234*:136-44, 1957.
22. Nalbandian, R. M., Gordon, S. and Kaufman, J. Calcium—digitalis tolerance test. A clinical report of the first 24 trials, *Amer. J. med. Sci. 234*:391-402, 1957.
23. Lown, B. and Levine, H. D. *Atrial arrhythmias, digitalis, and potassium.* New York, Landsberger Medical Books Inc., 1958.
24. Surawicz, B. and Lepeschkin, E. The electrocardiographic pattern of hypopotassemia with and without hypocalcemia, *Circulation 8*:801-28, 1953.
25. Kossmann, C. E. The effect of myocardial disease and dysfunction on the form of the electrocardiogram, *Trans. Life Insce. med. Dir. Amer. 41*:101-31, 1957.
26. Levine, H. D., Wanzer, S. H. and Merrill, J. P. Dialyzable currents of injury in potassium intoxication resembling acute myocardial infarction or pericarditis, *Circulation 13*:29-36, 1956.
27. Kleinfeld, M., Greene, H., Stein, E. and Magin, J. Effect of cadmium ion on the electrical and mechanical activity of the frog heart, *Amer. J. Physiol. 181*:35-38, 1955.
28. Stein, E., Kleinfeld, M., Greene, H. and Meyers, S. Action of lithium chloride on the isolated perfused frog heart, *Amer. J. Physiol. 183*:121-24, 1955.
29. Szekely, P. and Wynne, N. A. The effects of magnesium on cardiac arrhythmias caused by digitalis, *Clin. Sci. 10*:241-53, 1951.
30. Hoffman, B. F. and Suckling, E. E. Effect of several cations on transmembrane potentials of cardiac muscle, *Amer. J. Physiol. 186*:317-24, 1956.
31. Garb, S. The effects of potassium, ammonium, calcium, strontium, and magnesium on the electrogram and myogram of mammalian heart muscle, *J. Pharmacol. 101*:317-26, 1951.